Heterogeneities in confined water and protein hydration water

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Abstract
We report recent efforts to understand a broad range of experiments on confined water and
protein hydration water, many initiated by a collaboration between workers at the University of
Messina and MIT—the editors of this special issue. Preliminary calculations are not
inconsistent with one tentative interpretation of these experiments as resulting from the system
passing from the high-temperature high-pressure 'HDL' side of the Widom line (where the
liquid might display non-Arrhenius behavior) to the low-temperature low-pressure 'LDL' side
of the Widom line (where the liquid might display Arrhenius behavior). The Widom
line—defined to be the line in the pressure–temperature plane where the correlation length has
its maximum—arises if there is a critical point. Hence, interpreting the Messina–MIT
experiments in terms of a Widom line is of potential relevance to testing, experimentally, the
hypothesis that water displays a liquid–liquid critical point.

(Some figures in this article are in colour only in the electronic version)

Dedicated to Professor Francesco Mallamace, University of Messina, on the occasion of his
60th birthday

1. Introduction

One 'mysterious' property of liquid water was recognized 300 years ago [1]: although most liquids contract as temperature decreases, liquid bulk water begins to expand when its temperature drops below 4 °C. Indeed, a simple kitchen experiment demonstrates that the bottom layer of a glass of unstirred iced water remains at 4 °C while colder layers of 0 °C water 'float' on top (cf figure 1, and also figure 1 of [2]). The mysterious properties of liquid bulk water become more pronounced in the supercooled region below 0 °C [3–6]. For example, if the coefficient of thermal expansion α_P, isothermal compressibility K_T and constant-pressure specific heat C_P are

extrapolated below the lowest temperatures measurable they would become infinite at a temperature of $T_s \approx 228$ K [4, 7].

Water is a liquid, but glassy water—also called amorphous ice—can exist when the temperature drops below the glass transition temperature T_g. Although it is a solid, its structure exhibits a disordered molecular liquid-like arrangement. *Low-density* amorphous ice (LDA) has been known for 60 years [8], and a second kind of amorphous ice, *high-density* amorphous ice (HDA), was discovered in 1984 [9–11]. HDA has a structure similar to that of high-pressure liquid water, suggesting that HDA may be a glassy form of high-pressure water [12, 13], just as LDA may be a glassy form of low-pressure water. Water has at least two different amorphous
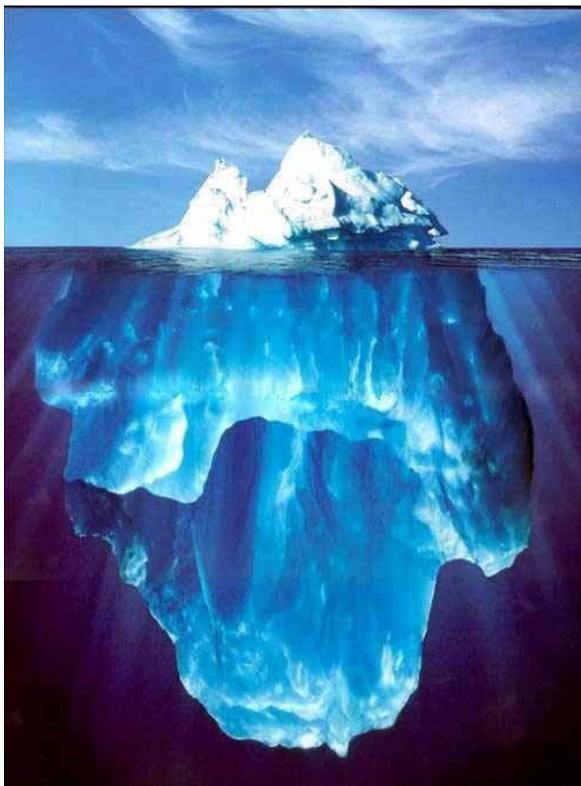
Figure 1. One of the 64 documented water anomalies (for the other 63 see, e.g., www.lsbu.ac.uk/water/anmlies.html). This anomaly is known to all who sailed in the *Titanic*: only 10% of the ice is above the surface. Courtesy of Professor M C Barbosa.

solid forms, a phenomenon called *polyamorphism* [14–20], and recently additional forms of glassy water have been the focus of active experimental and computational investigation [21–29].

2. Current hypotheses

Many classic 'explanations' for the mysterious behavior of liquid bulk water have been developed [30–35], including a simple two-state model dating back to Röntgen [36] and a clathrate model dating back to Pauling [37]. Three hypotheses are under current discussion:

(i) The *stability limit hypothesis* [38], which assumes that the spinodal temperature line $T_s(P)$ in the pressure–temperature (P–T) phase diagram connects at negative P to the locus of the liquid-to-gas spinodal for superheated bulk water. Liquid water cannot exist when cooled or stretched beyond the line $T_s(P)$.

(ii) The *singularity-free hypothesis* [39], considers the possibility that the observed polyamorphic changes in water resemble a genuine transition, but are not. For example, if water is a locally structured transient gel comprised of molecules held together by hydrogen bonds whose number increases as temperature decreases [40], then the local 'patches' or bonded sub-domains [41, 42] lead to enhanced fluctuations of specific volume and entropy and negative cross-correlations of volume and

entropy whose anomalies closely match those observed experimentally.

(iii) The *liquid–liquid (LL) phase transition hypothesis* [43] arose from MD studies on the structure and equation of state of supercooled bulk water and has received some support [44–48]. Below the hypothesized *second* critical point the liquid phase separates into two distinct liquid phases: a low-density liquid (LDL) phase at low pressures and a high-density liquid (HDL) at high pressure (figure 1). Bulk water near the known critical point at 647 K is a fluctuating mixture of molecules whose local structures resemble the liquid and gas phases. Similarly, bulk water near the hypothesized LL critical point is a fluctuating mixture of molecules whose local structures resemble the two phases, LDL and HDL. These enhanced fluctuations influence the properties of liquid bulk water, thereby leading to anomalous behavior.

One of the most remarkable physical and chemical phenomena is that of a critical point. One finds a single phase above a critical point (e.g. 'gas') but below it there exist two phases, distinct from each other by differing values of the specific volume and entropy—which are the two first partial derivatives of the Gibbs potential $G = G(P, T)$, where P denotes the pressure and T the temperature.

These two phases are physically distinguishable only if one considers thermodynamic paths that cross a specific line, called a first-order phase transition line. Along such paths, theoretical models exhibit a non-analytic 'jump discontinuity' in the first derivatives of $G = G(P, T)$. Specifically, the volume $V = (\partial G/\partial P)_T$, instead of decreasing smoothly with pressure (as it must!), jumps *discontinuously* by an amount ΔV, where $\Delta V \rightarrow 0$ as the critical point is approached. Similarly the entropy $S = (\partial G/\partial T)_P$, instead of increasing (as it must!) smoothly with temperature, jumps *discontinuously* by an amount ΔS, where $\Delta S \rightarrow 0$ as the critical point is approached.

The sign of the quantity $\Delta S/\Delta V$ determines the slope $(\partial P/\partial T)$ of the line of the first-order phase transition, due to the Clapeyron equation

$$\partial P/\partial T = \Delta S/\Delta V. \qquad (1)$$

The above remarks pertain to analytic solutions of model systems displaying critical points. Experimentally, it is not easy to identify the line of first-order phase transitions due to a set of phenomena that fall under the general term 'metastability'. For bulk water, it is possible to cool down to the homogeneous nucleation temperature T_H, approximately 235 K, before the liquid phase undergoes a first-order transition to a solid phase. For this reason, it is possible to study the properties of the liquid phase over a much broader temperature range. For confined water, and for protein hydration water, it appears possible to supercool well below 235 K as shown by Mallamace (University of Messina), to whom this conference is dedicated, and Chen (MIT). Their respective research groups have uncovered a rich set of both thermodynamic and dynamic phenomena which is being interpreted by them and by the Boston University group.

The most remarkable fact to emerge from the Mallamace–Chen experiments is that 'something happens' approximately 10 K lower than the homogeneous nucleation temperature of bulk water. There is no universal agreement on exactly how to interpret what is seen. One possibility is that the observed phenomena arise from the presence of a liquid–liquid (LL) critical point occurring at some temperature below the homogeneous nucleation temperature of the bulk liquid [2, 49–61, 40, 39, 62, 41, 63–67, 43, 68–75].

While this interpretation is consistent with the experimental data, it defies our intuition since fluid phase transitions normally separate into distinct liquid and gas phases, not two different liquids. However, the physical mechanism of the separation of a single-component fluid into a liquid and a gas applies equally to the separation of a single-component liquid into a high-density liquid (HDL) and a low-density liquid (LDL).

Why is this? The single attractive well in the intermolecular potential, no matter how shallow, implies that at sufficiently low temperatures the depth of the well normalized by T will be of sufficient size to generate a phase transition (figure 2(a)). Thus, for example, there are no 'permanent gases' (materials which cannot condense) despite what was once believed. Similarly, there are no perfect paramagnets (collections of spins that do not order), since again no matter how weak the spin–spin interaction is at sufficiently low temperatures, long-range order will arise.

Now consider a liquid whose potential, instead of *one* minimum (as in the Lennard-Jones potential) with one characteristic energy scale, has *two* minima (figure 2(b)). Such a situation could occur for a liquid with tetrahedral local symmetry, such as Si, SiO_2, P or water. Two such molecules experience an interaction energy that depends on their mutual orientation. If their mutual orientation resembles that of atmospheric pressure ice I_h, then the energy has one value which, at ambient pressure, is the lowest energy. However, at very high pressure the minimum energy occurs when one molecule is rotated 90° with respect to its neighbor (figure 2(c)). Such a 'tango configuration' has its energy minimum at a distance approximately 10% smaller than that of ice I_h. The above argument is supported by the fact that the solid phases of water include not only ice I_h but also ice VI, approximately 30% more dense than ice I_h.

The LL critical point hypothesis has the feature that, if it were valid, it would connect the anomalies of water, such as the presence of not one but rather two forms of glassy water. Others [76–93, 24, 25] have begun to test the possible validity of this still rather tentative conjecture [73, 94–112, 109, 113–125].

To understand 'why' water might display such a strange feature, which Stuart Rice calls *liquid polymorphism* [59], we have attempted to create various tractable models that display an LL phase transition, and to find solutions of these models using both analytic solutions of the simplest cases and approximate solutions (such as by integral equation approaches) for the more complex cases. Results thus far are not definitive, and one goal of our current research is to attempt to seek new avenues whereby definitive work can be undertaken to test the truth or falsehood of the LL critical point hypothesis.
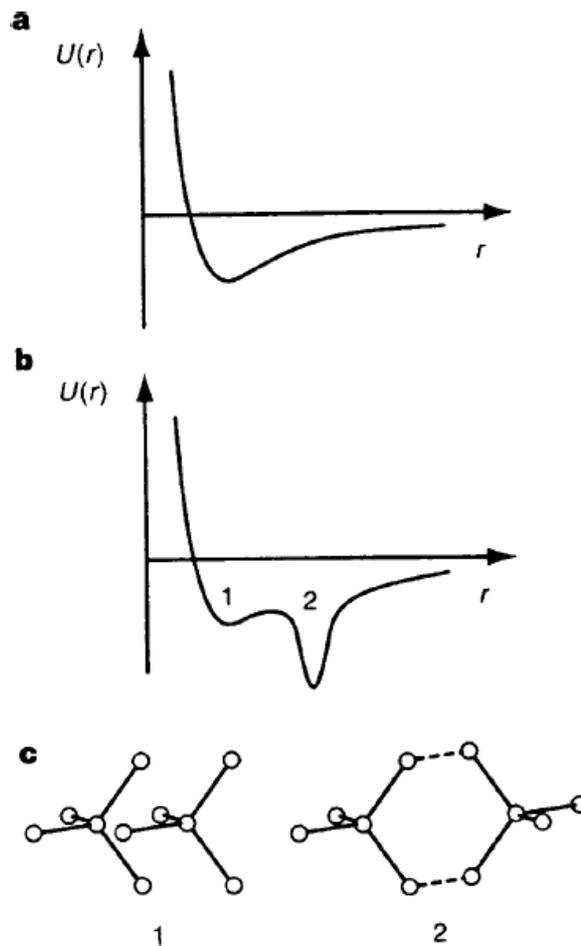
Figure 2. (a) An idealized system characterized by a pair interaction potential with a single attractive well. At low enough T ($T < T_c$) and high enough P ($P > P_c$), the system condenses into the 'liquid' well shown. (b) An idealized system characterized by a pair interaction potential whose attractive well has two sub-wells, the outer of which is deeper and narrower. For low enough T ($T < T_{c'}$) and low enough P ($P < P_{c'}$), the one-phase liquid can 'condense' into the narrow outer 'LDL' sub-well, thereby giving rise to an LDL phase, and leaving behind the high-density liquid phase occupying predominantly the inner sub-well. (c) Two idealized interaction clusters of water molecules in configurations that may correspond to the two sub-wells of (b).

3. Indirect experimental probe of the region below T_H ('no-man's land')

Mishima used a new method to probe the region below T_H and so provided a test for the hypothesized LL transition [81]. This paper—and its sequel for heavy water [82]—provide an indirect experimental probe of a large region of the P–T phase diagram that previously could not be explored, the region below T_H. This 'no-man's land' is of considerable general interest because the hypothesized LL critical point, if it exists at all, is believed to lie in this region. Reference [81] found that, along the decompression-induced melting (DIM) line of ice IV, a discontinuity in the slope occurs, a significant finding since a melting line must have a smooth behavior unless it intersects some other relevant line in the phase diagram such as a line of LL phase transitions. Mishima measured metastable DIM
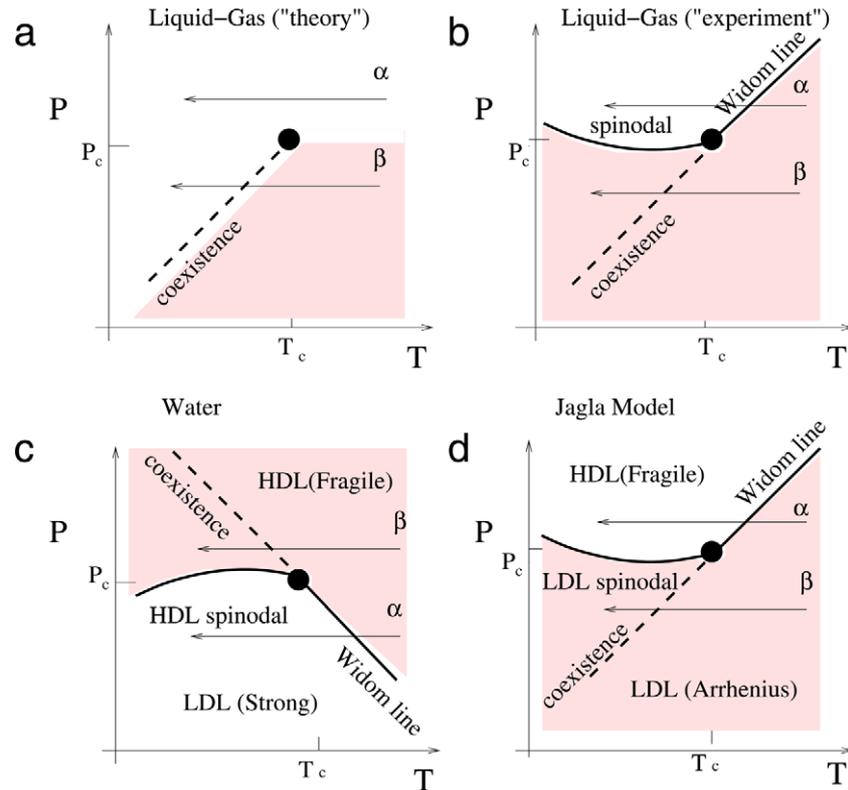
Figure 3. (a) Schematic phase diagram for the critical region associated with a liquid–gas critical point. Two features display mathematical singularities: the critical point and the liquid–gas coexistence. (b) The same, with the addition of the gas–liquid spinodal and the Widom line. Along the Widom line, thermodynamic response functions have extrema in their T dependence. (c) A hypothetical phase diagram for water of possible relevance to recent confined water neutron scattering experiments [87, 84, 226, 83]. (d) A sketch of the P–T phase diagram for the two-scale Jagla model. Adapted from [72].

curves of other high-pressure forms of ice and constructed the Gibbs potential surface of the liquid by knowing the Gibbs potential of the melting lines of each of the high-pressure ices and then interpolating between this set of lines. He found that a 'crease' emerges on the Gibbs potential surface of the liquid. Accordingly, a large volume change appears in the equation of state $V(P, T)$ of liquid, given by the pressure derivative $\partial G/\partial P$. Moreover, the location of the kink in the DIM line of ice IV is exactly the same as the location of the LL transition on the Gibbs surface.

The LL critical point hypothesis is of interest outside the domain of confined water because the underlying mechanism responsible for the LL phase transition suggests that, for other liquids with local tetrahedral symmetry, analogous *anticorrelated* entropy/volume heterogeneities could appear and might indeed, under appropriate conditions, condense out as a low-density liquid phase [92, 126]. This possibility has motivated high-quality work on other materials [127–138] such as Si, SiO_2, C and P. For P [128, 138], the line of LL phase transitions has been probed experimentally. Recent experiments detect a first-order LL phase transition in yttrium oxide–aluminum oxide melts [139]. Thus it is quite possible that the LL critical point hypothesis fails for water, but nonetheless could prove useful in guiding research on other materials [132, 55].

4. Direct experimental probe of the 'no-man's land' region for confined water

Recently, the MIT group of Professor S-H Chen and the Messina group of F Mallamace succeeded in probing the no-man's land by using the trick of confining liquid water to nanopores of diameters 16–20 Å [83, 84, 140–144]. The Boston University group, in collaboration with the MIT and Messina groups, performed calculations on models of bulk water and offered a possible interpretation of their experimental results [72]. The experimental results have also very recently been confirmed for confined water by Gallo *et al* [145]. Specifically, both groups found a correlation between the dynamic fragility transition and the 'Widom line', which is defined as the locus of correlation length maxima emanating from the hypothesized LL critical point of water [72]. Response functions are proportional to powers of the correlation length, and indeed one finds that the Widom line becomes asymptotically close to the loci of specific heat maxima C_P^{max} and thermal expansion coefficient maxima α_P^{max} [106, 110, 146, 147].

The preliminary findings of Xu *et al* [72] are consistent with a possible relation between the hypothesized LL critical point and the transition in the dynamics recently observed in neutron scattering experiments on confined water. More generally, they are finding that this connection between C_P^{max}

and the dynamic crossover may not be limited to the case of water, a hydrogen bond network forming liquid, but could be a more general feature of crossing the Widom line, and can also apply to confined water.

The conjectured interpretation of the MIT–Messina experiments relies on the concept of the Widom line, a concept not widely appreciated even though it has been known by experimentalists dating back to the 1958 PhD thesis of Levelt (now Levelt-Sengers) [148]. Since a Widom line arises only from a critical point, if the MIT–Messina experiments can be rationalized by a Widom line then they are consistent with the existence of an LL critical point in confined water [72].

By definition, in a first-order phase transition, thermodynamic functions discontinuously change as we cool the system along a path crossing the equilibrium coexistence line (figure 3(a), path β). However, in a *real* experiment, this discontinuous change may not occur at the coexistence line since a substance can remain in a supercooled metastable phase until a limit of stability (a spinodal) is reached [5] (figure 3(b), path β).

If the system is cooled isobarically along a path above the critical pressure P_c (figure 3(b), path α), the state functions continuously change from the values characteristic of a high-temperature phase (gas) to those characteristic of a low-temperature phase (liquid). The thermodynamic response functions which are the derivatives of the state functions with respect to temperature (e.g. C_P) have maxima at temperatures denoted $T_{max}(P)$. Remarkably these maxima are still prominent far above the critical pressure [148, 149], and the values of the response functions at $T_{max}(P)$ (e.g. C_P^{max}) diverge as the critical point is approached. The lines of the maxima for different response functions asymptotically approach one another as the critical point is approached, since all response functions become expressible in terms of the correlation length. This asymptotic line is sometimes called the Widom line, and is often regarded as an extension of the coexistence line into the 'one-phase regime.'

Suppose now that the system is cooled at constant pressure P_0. (i) If $P_0 > P_c$ (figure 3(b), path α), experimentally measured quantities will change dramatically but continuously in the vicinity of the Widom line (with huge fluctuations as measured by, for example, C_P). (ii) If $P_0 < P_c$ (figure 3(b), path β), experimentally measured quantities will change discontinuously if the coexistence line is actually seen. However, the coexistence line can be difficult to detect in a pure system due to metastability, and changes will occur only when the spinodal is approached where the gas phase is no longer stable.

In the case of water—the most important solvent for biological functions [51, 150]—a significant change in dynamical properties has been suggested to take place in deeply supercooled states [151, 50, 152, 153]. Unlike other network-forming materials [154], water behaves as a fragile liquid in the experimentally accessible window [50, 155, 156]. Based on analogies with other network-forming liquids and with the thermodynamic properties of the amorphous forms of water, it has been suggested that, at ambient pressure, liquid water should show a crossover between fragile behavior at high T to strong behavior at low T [157, 152, 158–160] in the deep supercooled region of the phase diagram below the homogeneous nucleation line. This region may contain the hypothesized LL critical point [43], the terminal point of a line of first-order LL phase transitions. Recently, dynamic crossovers in confined water were studied experimentally [161, 162, 87, 83] since nucleation can be avoided in confined geometries. Also, a dynamic crossover has been associated with the LL phase transition in both silicon and silica [129, 163]. We offered a very tentative interpretation of the observed fragility transition in water as arising from crossing the Widom line emanating from the hypothesized LL critical point [163] (figure 3, path α).

5. NMR proton chemical shift measurements as a new method for estimating the configurational part of the heat capacity $C_P(T)$

Recently, Mallamace and collaborators performed NMR proton chemical shift measurements as a new method for estimating the configurational part of the heat capacity $C_P(T)$ [164–166]. This study introduces NMR proton chemical shift measurements as a new method for estimating the configurational part of the heat capacity $C_P(T)$ that results from the hydrogen bonding of the water molecules. To test this new method, they measured the water proton chemical shift as a function of temperature by using the same confining system of recent nanoconfinement experiments [83, 84, 167, 168, 72, 169]. Specifically, they measured using NMR the proton chemical shift δ of supercooled nanoconfined water in the temperature range 195 K $< T <$ 350 K. Since δ is directly connected to the magnetic shielding tensor, they discussed the data in terms of the local hydrogen bond geometry and order. They argue that the derivative $-(\partial \ln \delta / \partial T)_P$ should behave roughly as the constant-pressure specific heat $C_P(T)$, and they confirm this argument by detailed comparisons with literature values of $C_P(T)$ in the range 290–370 K. They found that $-(\partial \ln \delta / \partial T)_P$ displays a pronounced maximum upon crossing the locus of maximum correlation length at about 240 K, consistent with the LL critical point hypothesis for water, which predicts that $C_P(T)$ displays *a maximum on crossing the Widom line*. Because the NMR technique also gives the chemical shift of each sample nucleus with non-zero spin, such an approach may be applicable to more complex materials.

6. The possible relevance of the skin of water surrounding a macromolecule to its low-temperature glass transition

Both experiments and computer simulation studies have shown that hydrated proteins undergo a 'glass-like' transition near 200 K [170–172], above which proteins exhibit diffusive motion, and below which the proteins are trapped in harmonic modes. An important issue is to determine the effects of hydration water on this dynamical transition [173, 174]. Experiments and computer simulations suggested that, when

a protein is solvated, the protein glass transition is strongly coupled to the solvent, leading to the question of whether the protein glass transition is directly related to a dynamic transition in the surrounding solvent [175].

Using molecular dynamics simulations, Kumar and collaborators [176, 177] investigated the relation between the dynamic transitions of biomolecules (lysozyme and DNA) and the dynamic and thermodynamic properties of hydration water. They found that the dynamic transition of the macromolecules, sometimes called a 'protein glass transition', occurs at the temperature of dynamic crossover in the diffusivity of hydration water, and also coincides with the maxima of the isobaric specific heat C_P and the temperature derivative of the tetrahedral order parameter. They related these findings to the hypothesis of an LL critical point in water: their simulations are consistent with the possibility that the protein glass transition results from crossing the Widom line.

7. Translational and rotational dynamic heterogeneities

At temperatures where liquids have a diffusion constant similar to that of ambient temperature water, the translational and rotational diffusion, D_t and D_r, respectively, are well described by the Stokes–Einstein (SE) relation $D_t = k_B T / 6\pi \eta R$ and the Stokes–Einstein–Debye (SED) relation $D_r = k_B T / 8\pi \eta R^3$. Here T is the temperature, η is the viscosity, k_B is the Boltzmann constant and R is the 'molecular' radius. Recently, the limits of the SE and SED relations have been an active field of experimental [167, 178], theoretical [179–182] and computational [183–188, 169, 189] research. The general consensus is that the SE and SED relations hold for low-molecular-weight liquids for $T \geqslant 1.5T_g$, where T_g is the glass transition temperature. For $T \leqslant 1.5T_g$, deviations from either one or both of the SE and SED relations are observed. Experimentally, it is found that the SE relation holds for many liquids in their stable and weakly supercooled regimes, but when the liquid is deeply supercooled it overestimates D_t relative to η by as much as two or three orders of magnitude, a phenomenon usually referred to as the 'breakdown' of the SE relation. The situation for the SED relation is more complex. Some experimental studies found agreement with the predicted values of the SED relation even for deeply supercooled liquids, while others also claim a breakdown of the SED relation to the same extent as for the SE relation. The failure of these relations provides a clear indication of a fundamental change in the dynamics and relaxation of the system. Indeed, the changing dynamics of the liquid as it approaches the glass transition is well documented, but not yet fully understood [57, 190, 191].

There is a growing body of evidence [192, 193] that, upon cooling, a liquid does not become a glass in a spatially homogeneous fashion. Instead the system is characterized by the appearance of dynamical heterogeneities [192–194]. In the 'dynamical heterogeneities' view, the motion of atoms or molecules is highly spatially correlated. This phenomenon is often called 'spatially heterogeneous dynamics', since there are spatial regions in which the structural relaxation time can differ by orders of magnitude from the average over the entire system.

The presence of these dynamic heterogeneities has been argued to give rise to the breakdown of the SE relation [182]. Since the derivation of the Einstein relation assumes uncorrelated motion of particles, it is reasonable that the emergence of correlations could result in a failure of the SE relation. Our aim is to assess the validity of the SE and SED relations in the SPC/E model of water, and consider to what extent the dynamic heterogeneities contribute to the SE and SED breakdown.

Computer simulations have been particularly useful for studying dynamic heterogeneities (see, e.g., [195–200]) since simulations have direct access to the details of the molecular motion. For water, the existence of regions of enhanced or reduced mobility has also been identified [200]. In particular, [200] identifies the clusters of molecules with greater *translational* (or center-of-mass) mobility with the hypothesized 'cooperatively rearranging regions' of the Adam–Gibbs approach [201]. For water, those dynamic heterogeneities are also accompanied by spatial heterogeneities [122, 41].

Mazza and collaborators [202–206] found that both the SE and SED relations break down at low temperature. To explore the relationship between these breakdowns and dynamic heterogeneities, they also calculate the SE and SED relations for subsets of the 7% 'fastest' and 7% 'slowest' molecules. They found that the SE and SED relations break down in both subsets, and that the breakdowns occur on all scales of mobility. Thus these breakdowns appear to be generalized phenomena, in contrast to a view where only the most mobile molecules are the origin of the breakdown of the SE and SED relations, embedded in an inactive background where these relations hold. At low temperature, the SE and SED relations in both subsets of molecules are replaced with 'fractional' SE and SED relations, $D_t \sim (\tau/T)^{-\xi_t}$ and $D_r \sim (\tau/T)^{-\xi_r}$ where $\xi_t \approx 0.84$ (<1) and $\xi_r \approx 0.75$ (<1). They also found that there is a decoupling between rotational and translational motion, and that this decoupling occurs in both fastest and slowest subsets of molecules. Further, they found that, when the decoupling increases upon cooling, the probability of a molecule being classified as both translationally and rotationally fastest also increases. To study the effect of timescale for SE and SED breakdown and decoupling, they introduce a time-dependent version of the SE and SED relations, and a time-dependent function that measures the extent of decoupling. Their results suggest that both the decoupling and SE and SED breakdowns originate at the timescale corresponding to the end of the cage regime, when diffusion starts. This is also the timescale when the dynamic heterogeneities are more relevant.

8. The possible cause of the experimentally observed breakdown of the Stokes–Einstein relation

In their Cozzarelli-Prize winning paper, the MIT and Messina group's experiments very recently showed that supercooled water exhibits a breakdown of the SE relation between the diffusion constant D and the alpha relaxation time τ_α [167]. For simulated water, they found that the temperature of the decoupling of diffusion and alpha relaxation correlates with the temperature of the maximum in specific heat that occurs at the

Widom line $T_W(P)$. Specifically, they found that their results for $D\tau_\alpha/T$ collapse onto a single master curve if temperature is replaced by $T - T_W(P)$, where $T_W(P)$ is the temperature where the constant-pressure specific heat achieves a maximum. Moreover they found that the size of the mobile molecule clusters (dynamical heterogeneities) increases sharply near $T_W(P)$. The crossover from the less structured locally high-density liquid (HDL) environment at high T to the more structured locally low-density liquid (LDL) environment as $T \to T_W(P)$ appears to be correlated with both the breakdown of the SE relation and the growth of dynamic heterogeneities.

The breakdown of the SE relation is usually understood by the fact that diffusion at low temperatures is dominated by regions of fast moving molecules while the relaxation of the system as a whole is dominated by slow moving molecules. Consistent with this, Kumar *et al* [167, 169] found that the growth of mobile particle clusters occurs near the Widom line and the breakdown of the SE ratio for $P < P_c$. Thus the SE breakdown in water is consistent with the LL critical point hypothesis [81, 163, 54, 49, 50]. Their results are also consistent with recent experimental findings in confined water [83, 84, 167].

9. The appearance of the fractional Stokes–Einstein relation in water and a structural interpretation of its onset

Very recently, Mallamace and his collaborators presented experimental data on water demonstrating that, below a crossover temperature $T_\times \approx 290$ K, the SE relation is replaced by a 'fractional' SE relation $D \sim (\tau/T)^{-\zeta}$ with $\zeta \approx 3/5$ [207]. They interpreted the microscopic origin of this crossover by analyzing the OH stretch region of the FTIR spectrum over a wide T range from 350 K down to 200 K. Simultaneous with the onset of fractional SE behavior, they found that water begins to develop a local structure like that of LDA, low-density amorphous solid H_2O. Specifically, as a first step to obtain a structural interpretation of this fractional SE behavior, they studied the infrared spectrum. For water, this spectrum can be split into two contributions, one resembling the spectrum of high-density amorphous (HDA) solid H_2O and the other resembling the spectrum of LDA. They interpret these two contributions as corresponding to water molecules with more HDA-like local structure, or more LDA-like local structure, respectively. With decreasing T, the LDA-like population increases, while the HDA-like population decreases. The fractional SE crossover temperature $T_\times$ appears to roughly coincide with the onset of the increase of the population of molecules with LDA-like local structure (and a corresponding decrease of the population of the molecules with HDA-like local structure), consistent with the possibility that the changes in intramolecular vibrational properties may be connected to the onset of fractional SE behavior. Thus these data lead to an interpretation that the fractional SE relation in water arises from a specific change in local water structure. To further test this interpretation, they performed computer simulations of two molecular models, TIP5P and Jagla [121], and their simulation results supported the experimental observations.

10. Experimental method of testing the singularity-free scenario

Using Monte Carlo simulations and mean-field calculations Stokely *et al* [208] showed that a cell model of water proposed by Franzese *et al* [73, 75, 100] reproduces all four scenarios that have been discussed for water. Kumar *et al* [209–211] found that both the LL critical point and singularity-free (SF) scenarios exhibit a dynamic crossover at a temperature close to $T(C_P^{max})$, which decreases for increasing P. They interpret the dynamic crossover as a consequence of a local breaking and reorientation of the bonds for the formation of new and more tetrahedrally oriented bonds. Above $T(C_P^{max})$, when T decreases, the number of hydrogen bonds increases, giving rise to an increasing activation energy E_A and to a non-Arrhenius dynamics. As T decreases, entropy must decrease. A major contributor to entropy is the orientational disorder, which is a function of p_B, the probability of forming a hydrogen bond, as described by the mean-field expression for the entropy change ΔS with orientation. They found that, as T decreases, p_B increases. They found that the rate of increase has a maximum at $T(C_P^{max})$, and as T continues to decrease this rate drops rapidly to zero—meaning that, for $T < T(C_P^{max})$, the local order rapidly becomes temperature-independent and the activation energy E_A also becomes approximately temperature-independent. Corresponding to this fact the dynamics becomes approximately Arrhenius.

They found that the relaxation time at the crossover temperature T_A is approximately independent of the pressure (isochronic crossover), consistent with their calculations of an almost constant number of bonds at $T(C_P^{max})$. They found also that, in both scenarios, E_A and T_A decrease upon increasing P. Instead, the P dependence of the quantity $E_A/(k_B T_A)$ has a different behavior in the two scenarios. For the LL critical point scenario it increases as $P \to P_{c'}$, while it is approximately constant in the SF scenario. They interpret this difference as a consequence of the larger increase of the rate of change of p_B in the LL critical point scenario, where p_B diverges at finite $T_{c'}$, compared to the SF scenario, where p_B can possibly diverge only at $T = 0$. Experiments can detect local changes of water structure from HDL-like to LDL-like, (e.g. [212]). Hence, it is possible to test the predictions of the dynamic consequences of this local change. Franzese *et al* [213] found that three of the four predictions made by Kumar *et al* in [209, 210] are verified in experiments. Indeed, Chen and collaborators verified that the crossover is isochronic, and that E_A and T_A decrease upon increasing P. The fourth prediction, about the behavior of $E_A/(k_B T_A)$, discriminating between the two possible scenarios, cannot be verified within the precision of the experiment [214].

Recently, Mazza *et al* [215] extended to lower temperatures the Kumar *et al* [209, 210] analysis, using a cluster Monte Carlo simulation method [216]. They found that C_P has a second maximum at very low T, associated with the increase of tetrahedral order in the hydrogen bond network of water [215] and clarify that the maximum at higher T found by Kumar *et al* [209, 210] is associated with the maximum fluctuation of the hydrogen bond formation but not necessarily with a larger

tetrahedral order. They found that the two maxima of C_P approach each other and merge when $P \to P_c$ and that the two maxima separate for $P > P_c$. When the two maxima of C_P merge, then the Widom line is correctly defined because the fluctuations of the LDL-like and HDL-like regions can spread along the entire system.

11. Ongoing work

When data begin to deviate from extrapolations there must be an underlying reason for the deviation. These deviations include phenomena at temperatures as high as 46 °C, 35 °C and 4 °C (sudden changes of the sign of the temperature derivatives of isothermal compressibility, isobaric specific heat and the sign of the coefficient of thermal expansion, respectively) [106, 110, 146, 147, 217]. Thus far there is no coherent and accepted explanation for these anomalies—even the anomalies that occur at biologically relevant temperatures. It is unfortunate that we cannot offer students a coherent explanation of water's behavior, even though water is 'essential for life,' and even though very small perturbations on pure water are incompatible with life (such as substituting water by heavy water).

One question we will focus on in ongoing work is 'what features of bulk water survive confinement'? Certainly the hydrogen bond network is perturbed, which explains why MCM-41 nanoconfined water remains liquid down to approximately 100 degrees lower than for bulk water. But what about the collective properties of water [218–222, 3, 223, 145, 224] which rely on the direct cooperative interactions among water molecules? How are these perturbed by confinement? For example, a confined magnet or fluid near its critical point behaves exactly as a bulk magnet or fluid until the system is so close to the critical point that its correlation length (the length scale over which the spins or molecules are correlated) increases to reach the size of the confining system. The MIT/Messina water experiments on MCM-41 confinement are typically carried out in tubes of diameter about 1.5–2.0 nm. Hence if we apply the principles of phase transition theory, the cooperative properties of the system may resemble those of a bulk system down to temperatures extremely close to the critical point.

Very recently Kumar and co-workers [225] introduced the space-dependent correlation function $C_Q(r)$ and time-dependent autocorrelation function $C_Q(t)$ of the local tetrahedral order parameter $Q \equiv Q(r, t)$. Using computer simulations of 512 water-like particles interacting through the TIP5P potential, they investigated $C_Q(r)$ in a broad region of the phase diagram. They found that at low temperatures $C_Q(t)$ exhibits a two-step time-dependent decay similar to the self-intermediate scattering function, and that the corresponding correlation time τ_Q displays a dynamic crossover from non-Arrhenius behavior for $T > T_W$ to Arrhenius behavior for $T < T_W$, where T_W denotes the Widom temperature where the correlation length has a maximum as T is decreased along a constant-pressure path. They defined a tetrahedral entropy S_Q associated with the *local* tetrahedral order of water molecules and find that it produces a major contribution to the specific heat maximum at the Widom line, and showed that τ_Q can be extracted from S_Q using an analogue of the Adam–Gibbs relation.

Also very recently, Mazza *et al* [227] studied the correlation time of the tetrahedral correlation function for the cell model, discussing the existence of not one, but two, dynamic crossovers in this correlation function. Using the Adam–Gibbs relation, they associated these two crossovers with the two maxima in C_P found in [215], offering an interpretation of the recent experimental observation of two dynamic crossovers in protein hydration water [227].

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